

Dr. Benjamin Tycko

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Physiological Functions of Imprinted Genes

Ben Tycko, Columbia University ICG



Epigenetics

Cell Memory



Rainbow Cat

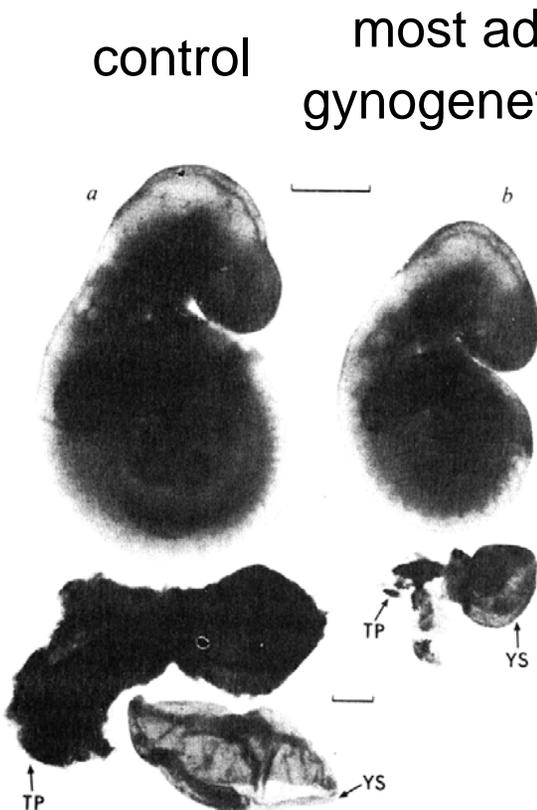


Copy Cat

Genomic Imprinting

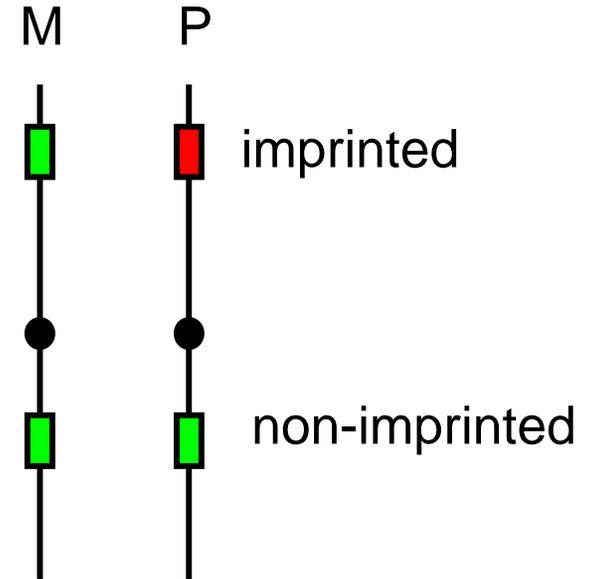
"Development of reconstituted mouse eggs suggests imprinting of the genome during gametogenesis"

Surani, Barton & Norris, Nature 308, 548-550 (1984)



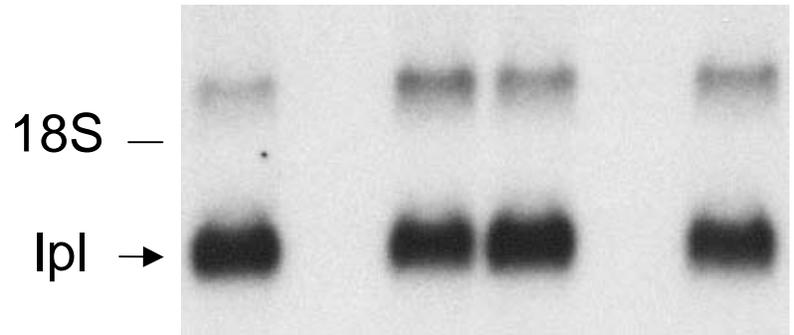
"Our model implies that the paternal and/or maternal genome (whole or in part) are somehow conditioned/alterd during gametogenesis and that this conditioning is completely reversible (as is the case for the X chromosome)."

McGrath & Solter, Cell 37, 179-183 (1984)

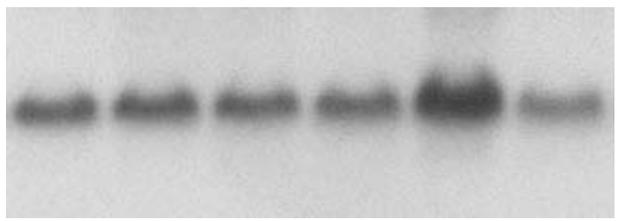


Genomic Imprinting: Gene Dosage

Genotype: +/+ +/- mat +/- pat +/+ -/- +/+



Ipl (imprinted gene)



Actin probe

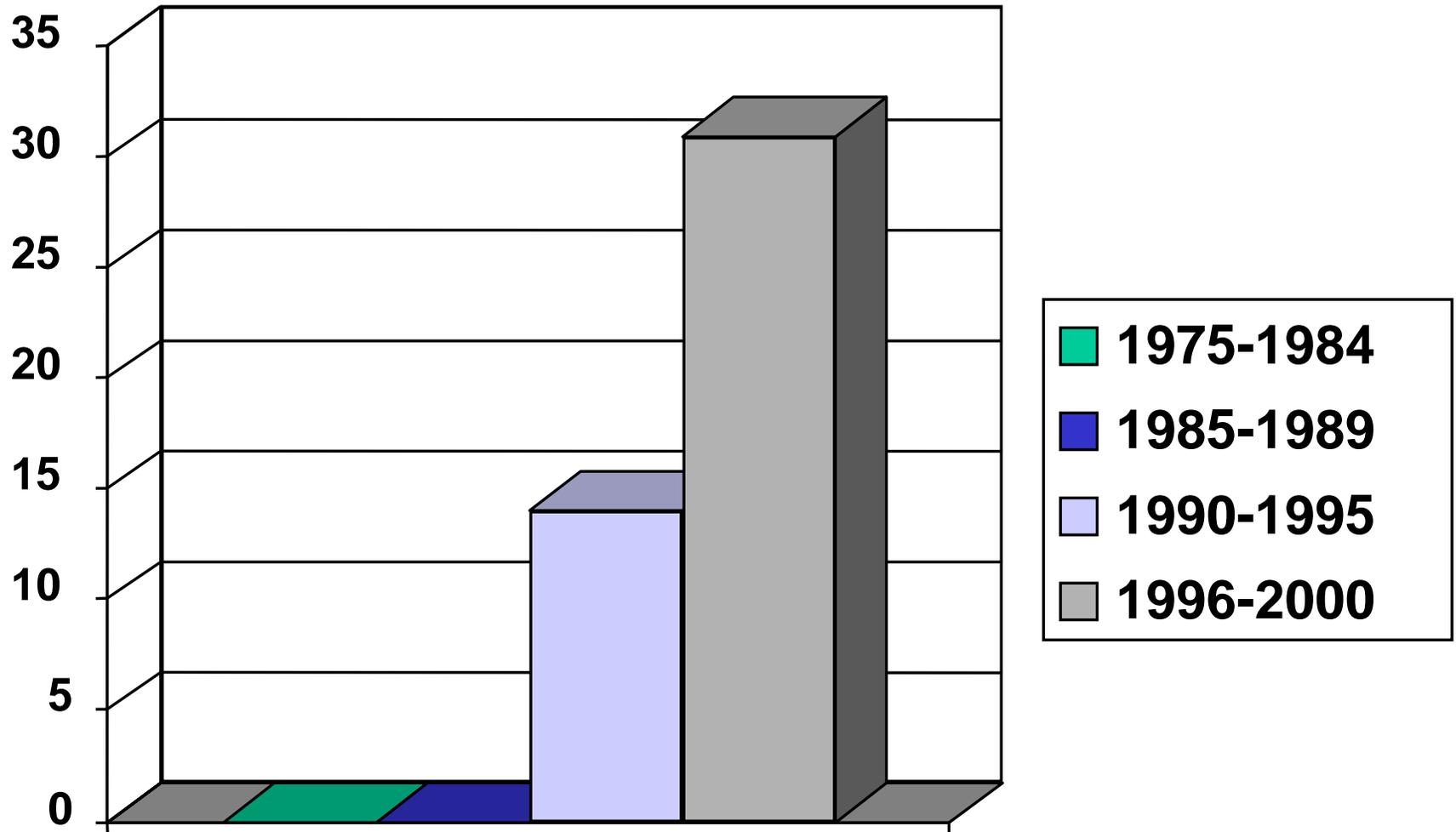
Theories of Imprinting

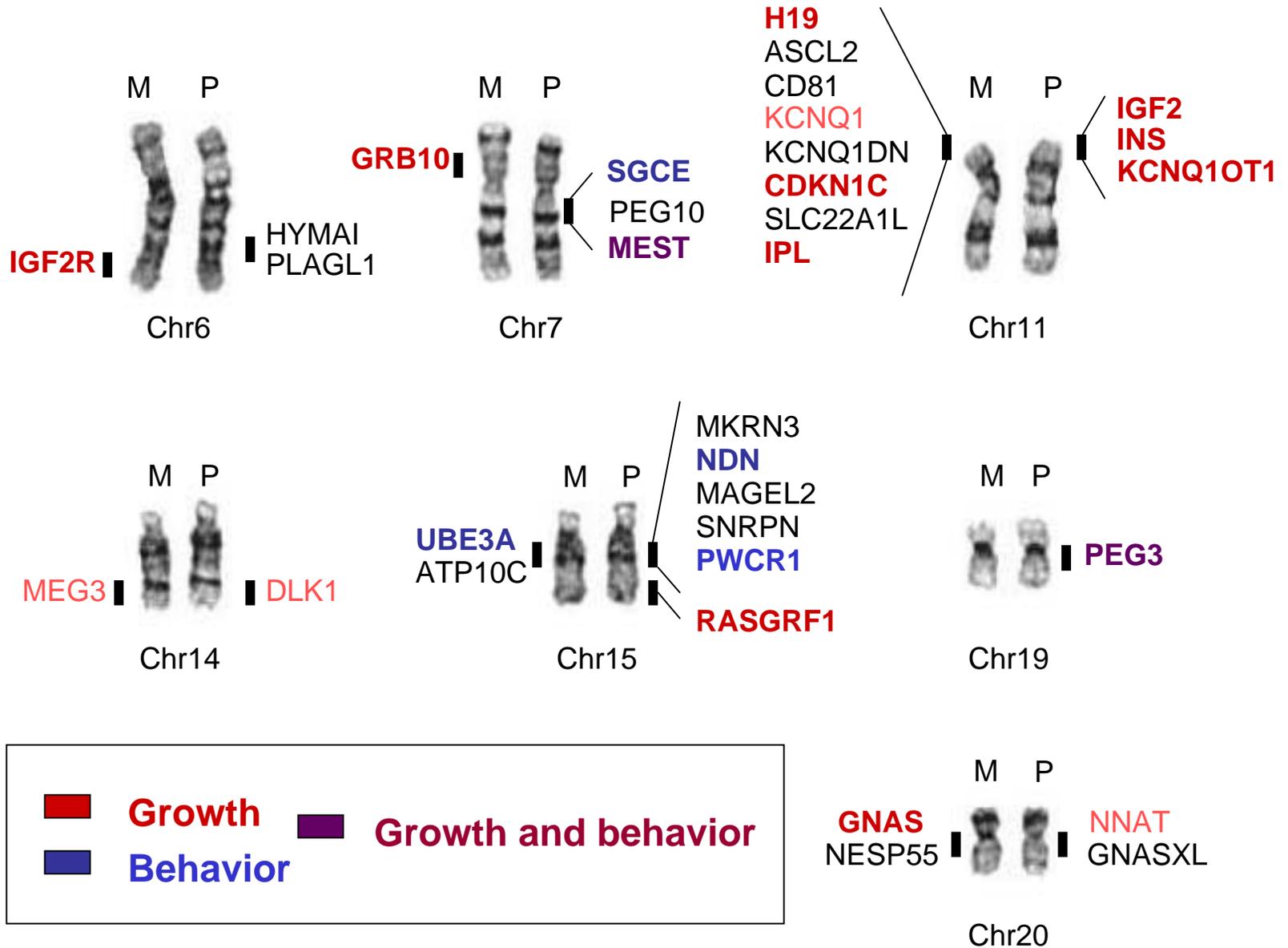
- Mechanism: locations of imprinted domains dictated by DNA methylation and regional chromatin structure in gametogenesis
 - *multiple imprinted genes clustered in megabase-scale regions*
 - *imprinting determined by allele-specific DNA methylation at critical sites*

Theories of Imprinting

- Mechanism: locations of imprinted domains dictated by DNA methylation and regional chromatin structure in gametogenesis
 - multiple imprinted genes clustered in megabase-scale regions*
 - imprinting determined by allele-specific DNA methylation at critical sites*
- Biological Function: conflict between maternal and paternal “drives” for reproductive success.
 - paternally silenced genes retard growth of the conceptus; maternally silenced genes promote growth and increase nutritional demands on the mother*

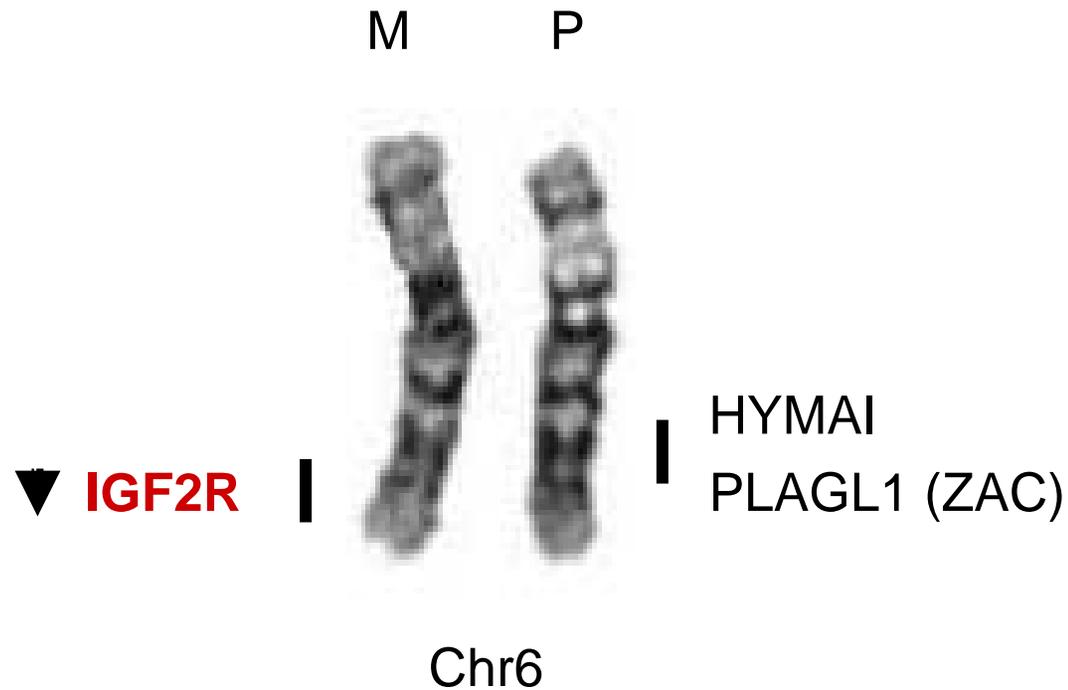
Imprinted Genes





Tycko and Morrison, J Cell Physiol, 2002

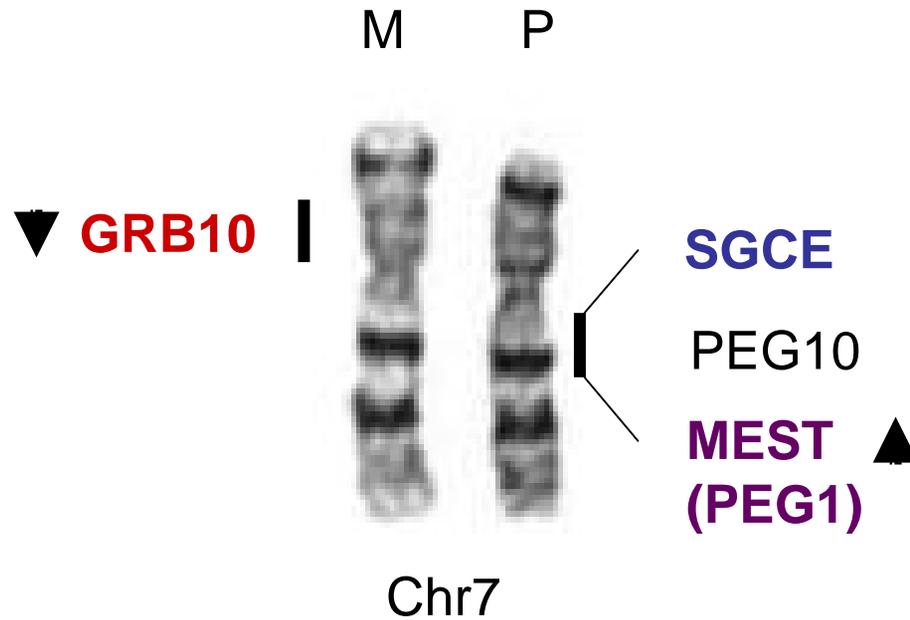
Imprinted genes on Mm17/Hs6



	Growth		Growth and behavior
	Behavior		

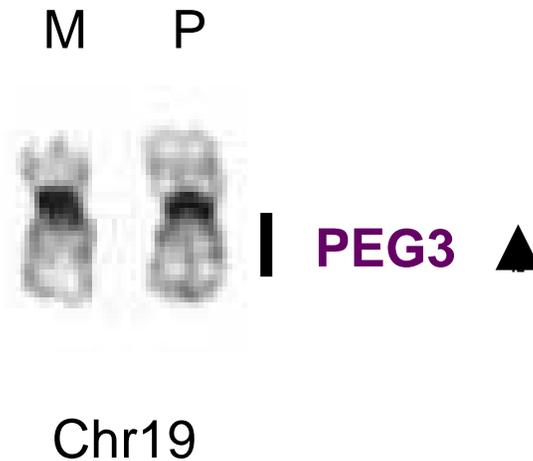
▼ ▲ Effect on growth

Imprinted genes on Mm11/Hs7



▼ ▲ Effect on growth

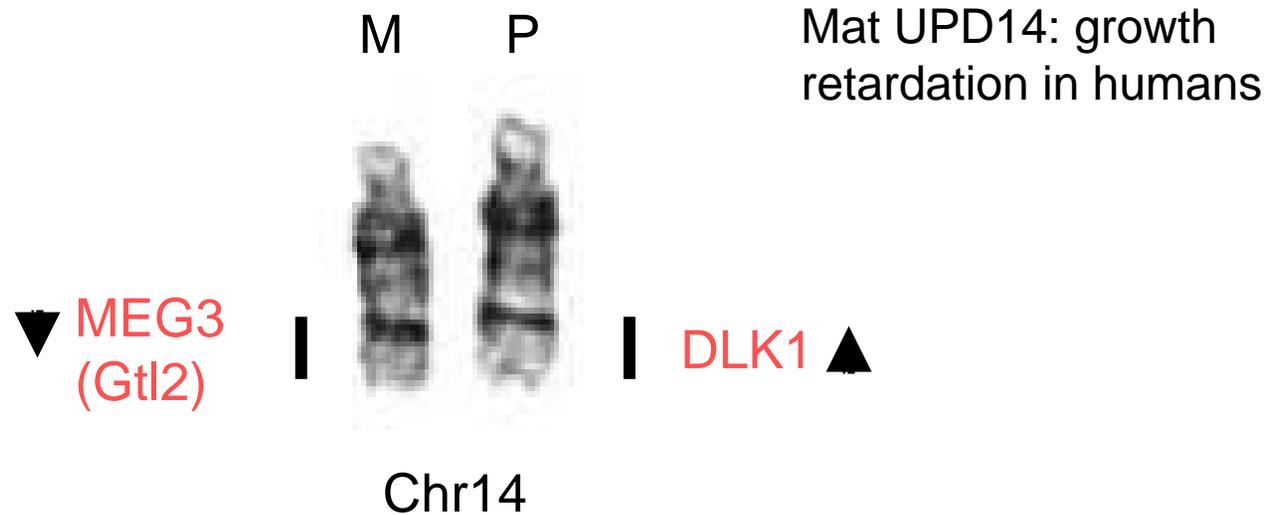
Imprinted Genes on Hs19q/Mm7



	Growth		Growth and behavior
	Behavior		

▼ ▲ Effect on growth

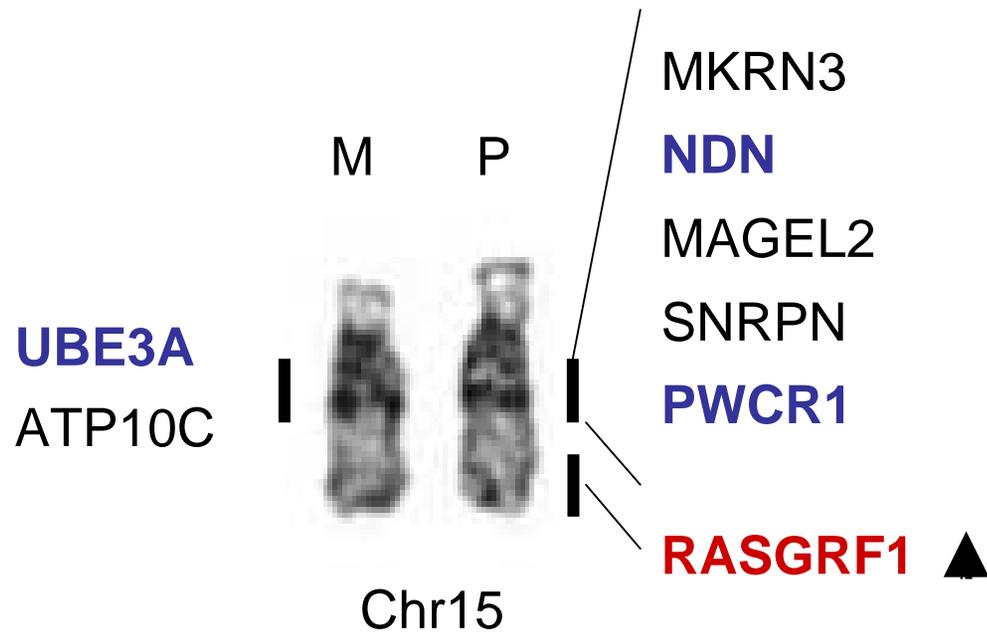
Imprinted Genes on Hs14q32/Mm12



	Growth		Growth and behavior
	Behavior		

▼ ▲ Effect on growth

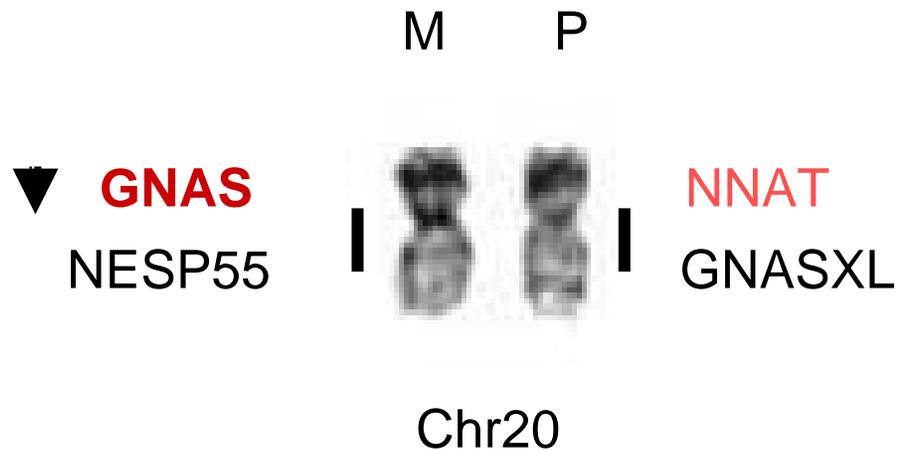
Imprinted Genes on Hs15q/Mm7



	Growth		Growth and behavior
	Behavior		

▼ ▲ Effect on growth

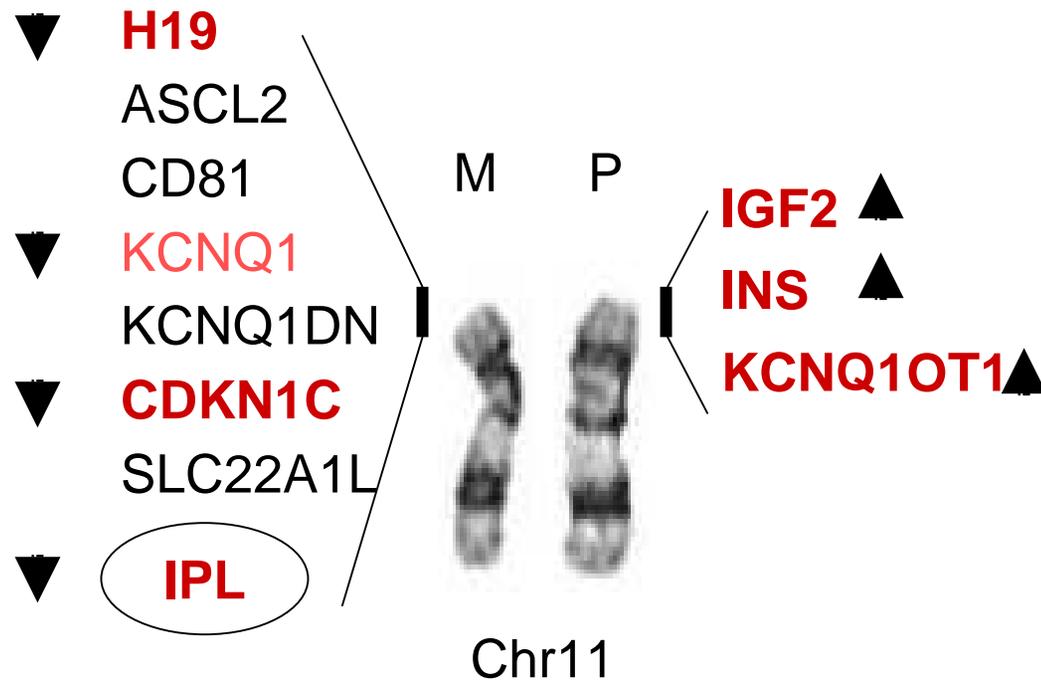
Imprinted Genes on Hs20q/Mm2



	Growth		Growth and behavior
	Behavior		

▼ ▲ Effect on growth

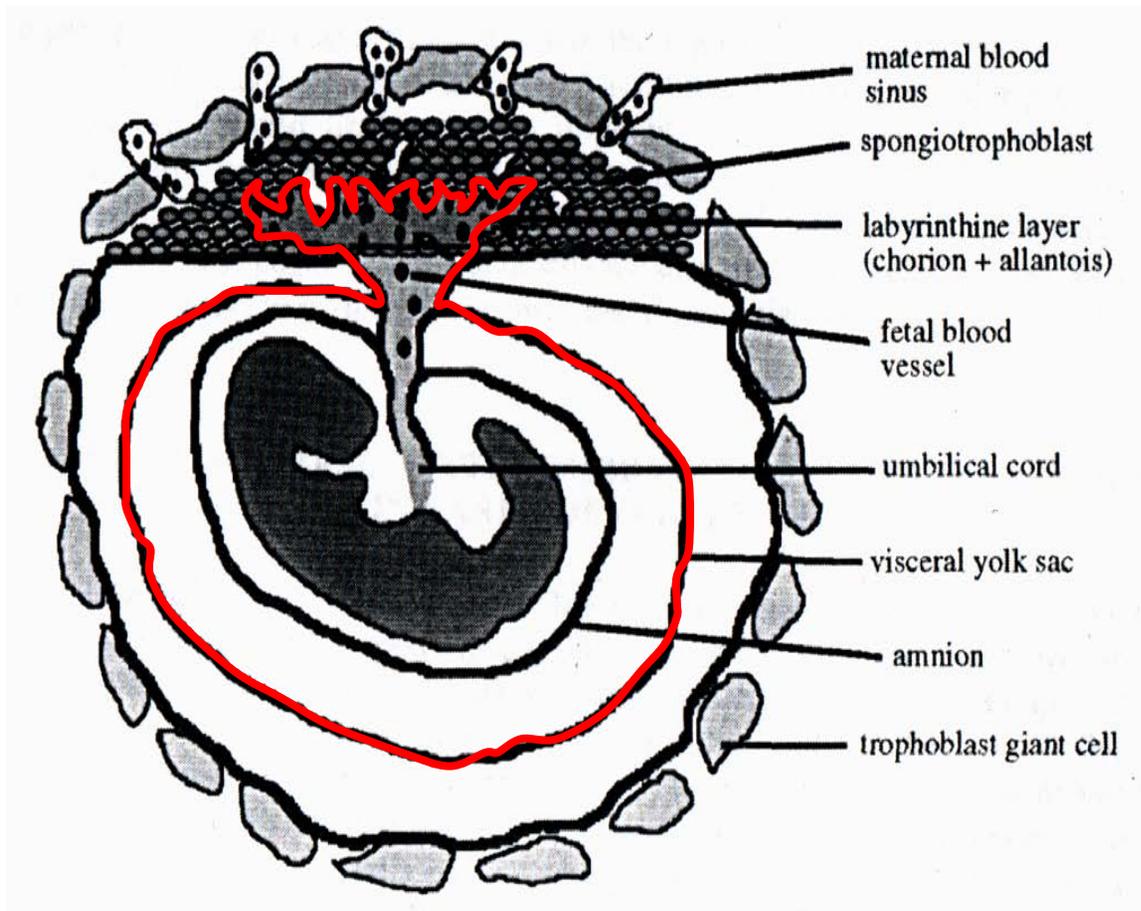
Imprinted Genes on Hs11p15/Mm7



	Growth		Growth and behavior
	Behavior		

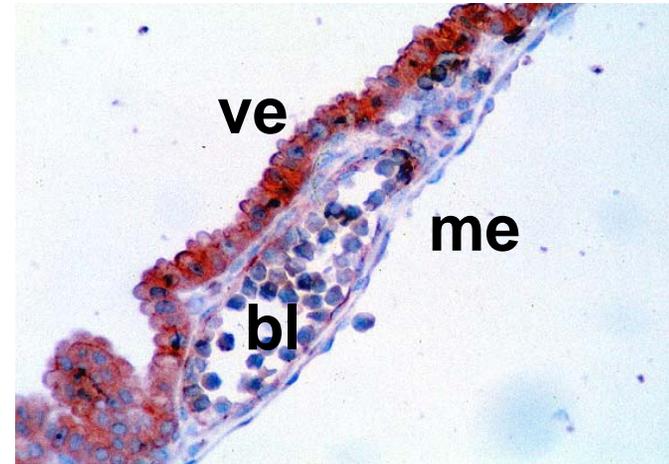
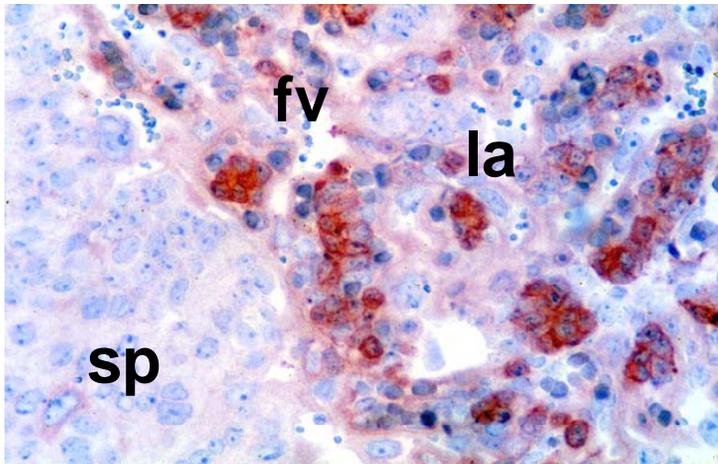
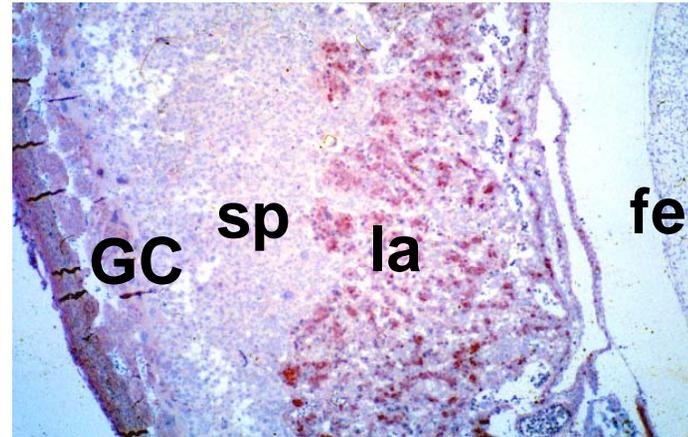
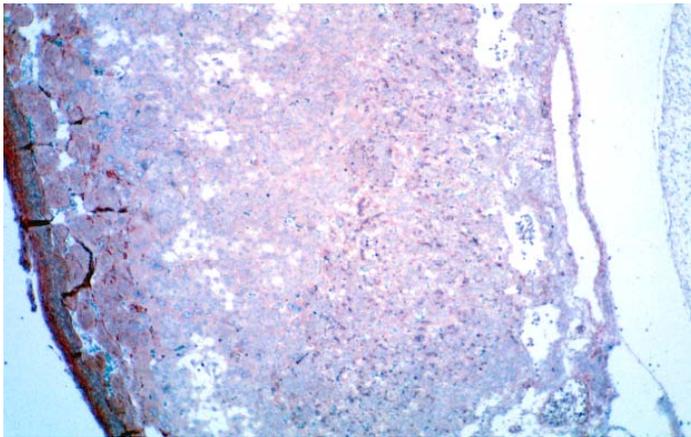
▼ ▲ Effect on growth

Feto-Maternal Interaction: Extraembryonic Tissues

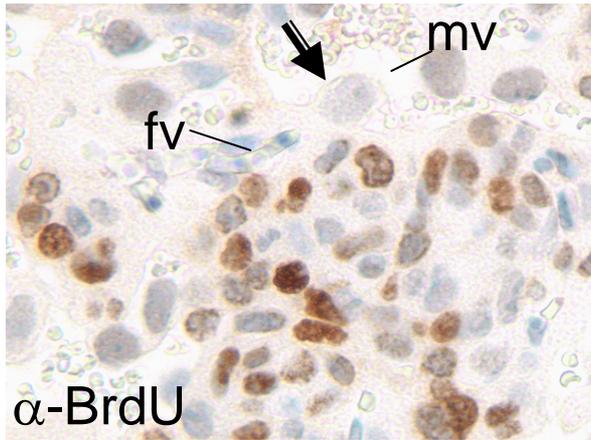
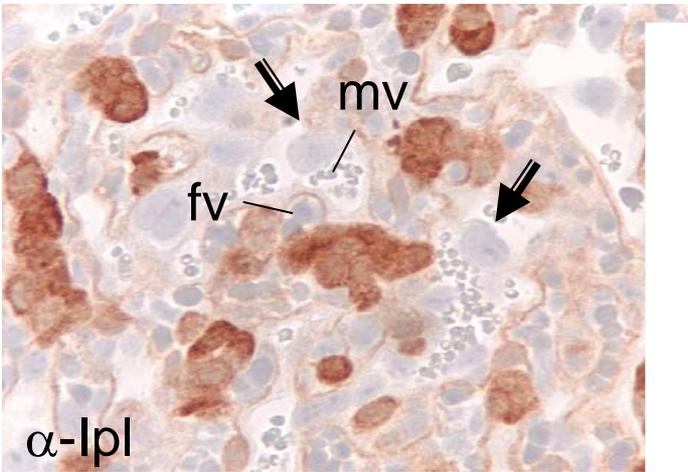
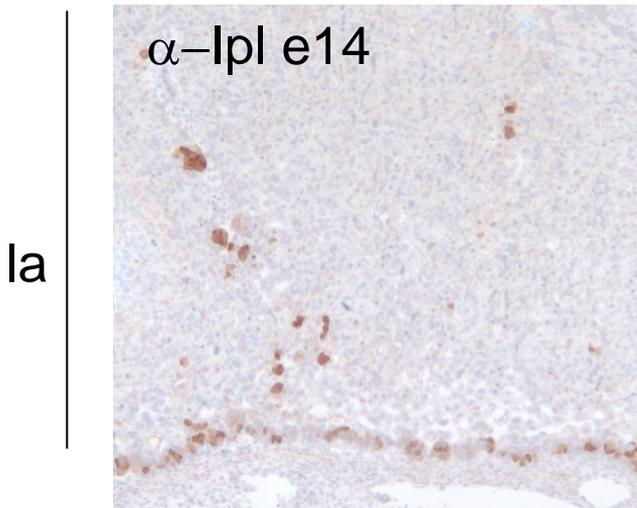
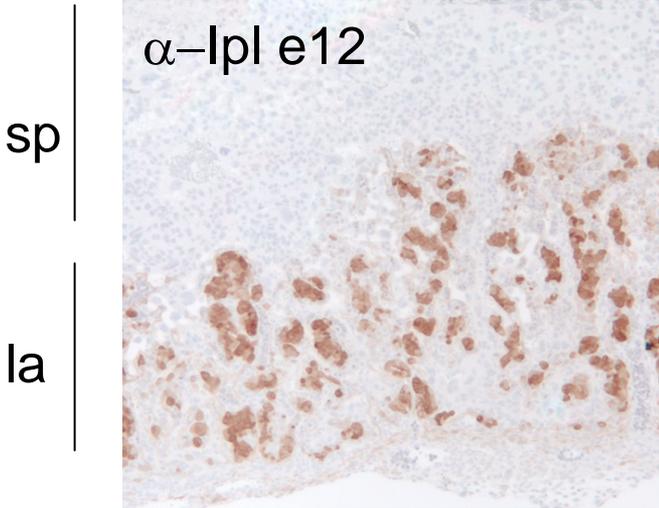


[Cross, J.C., Annals NY Acad Sci]

Expression of *lpl* in Extraembryonic Tissues

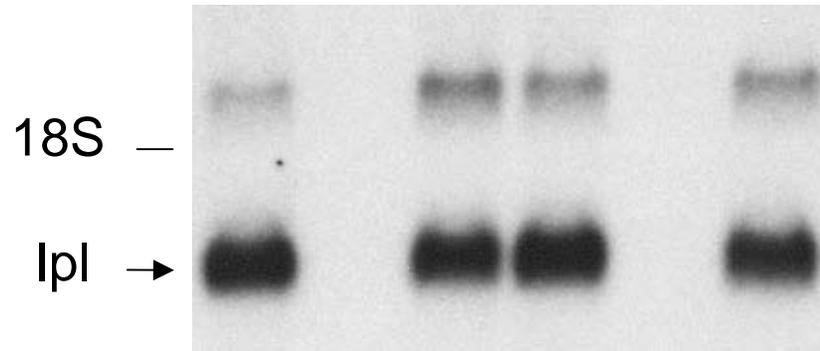


Ipl-positive cells disappear at mid→late gestation

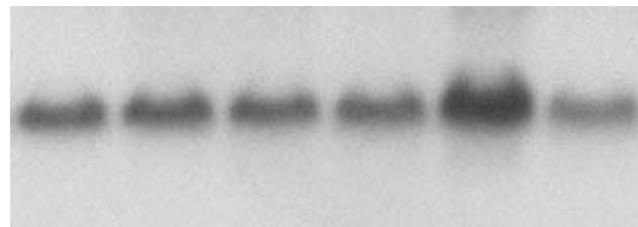


Ipl KO mice

Genotype: $+/+$ $+/-$ $+/-$ $+/+$ $-/-$ $+/+$
 mat pat

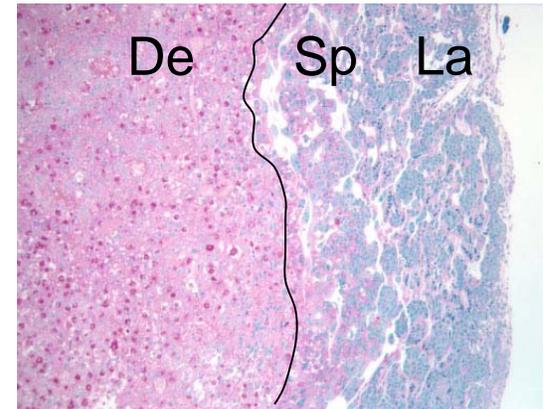
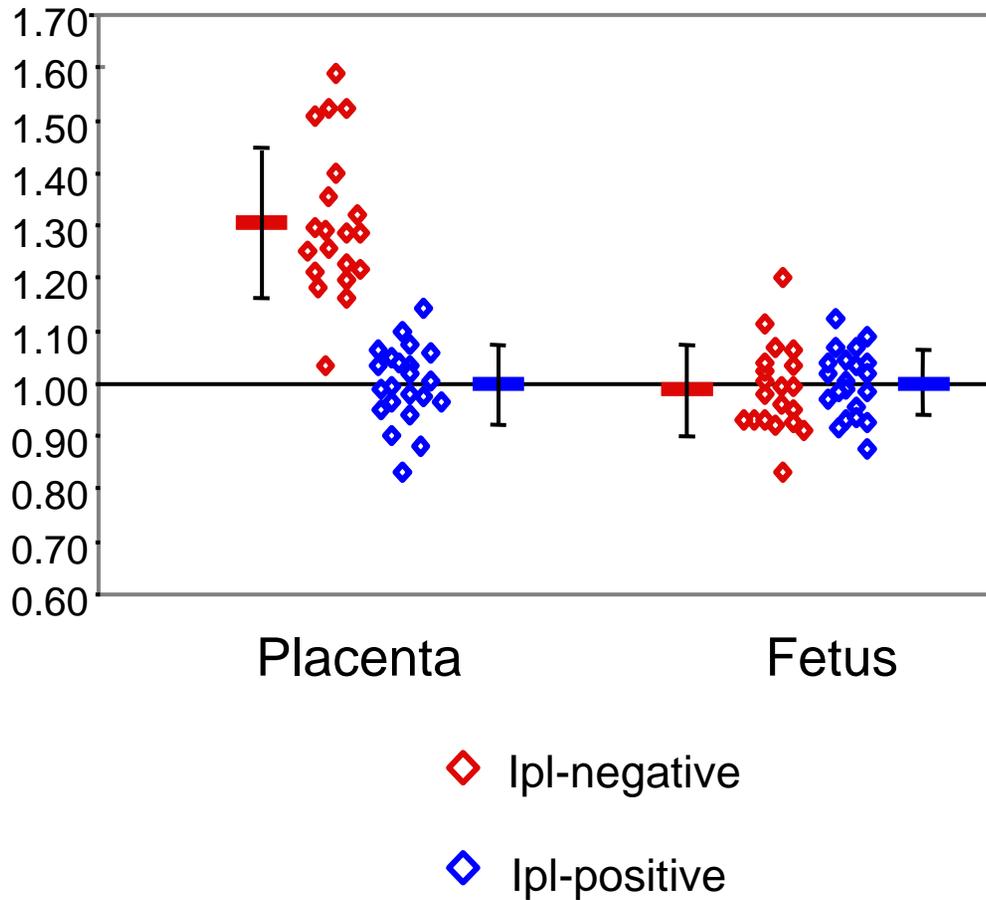


Ipl (imprinted gene): cDNA probe

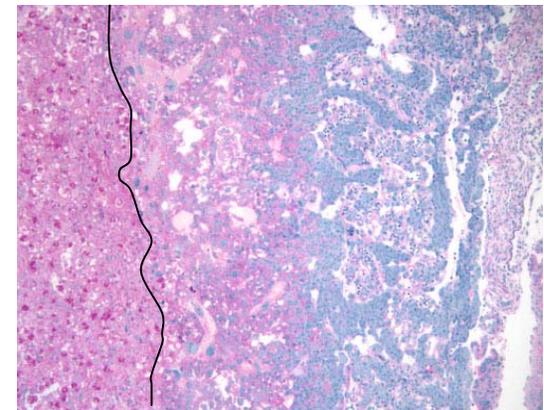


Actin probe

Placental Overgrowth in *Ipl* KO Mice

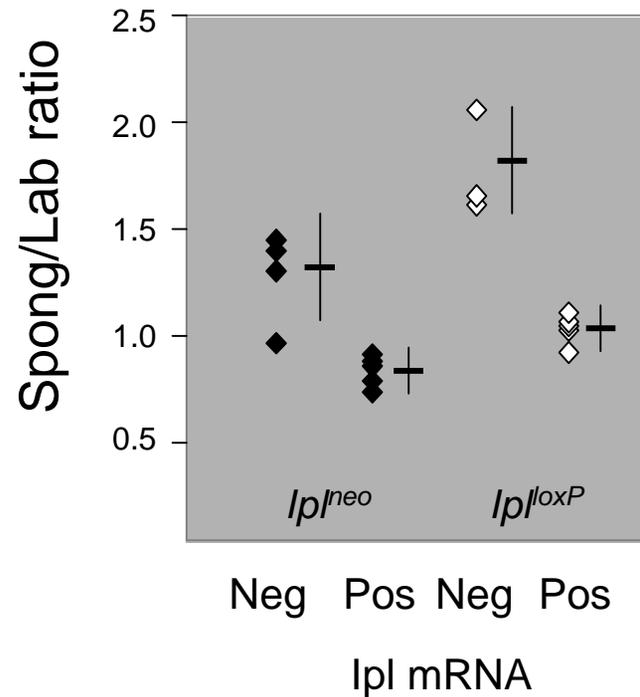
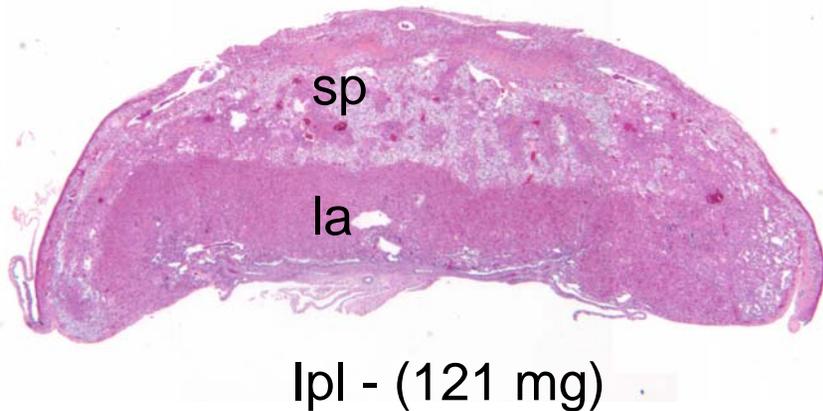
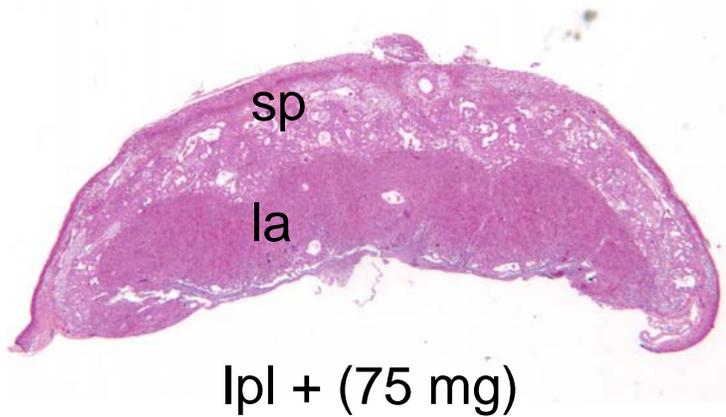


Ipl-positive

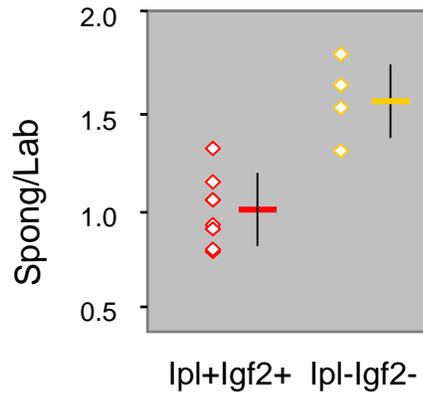
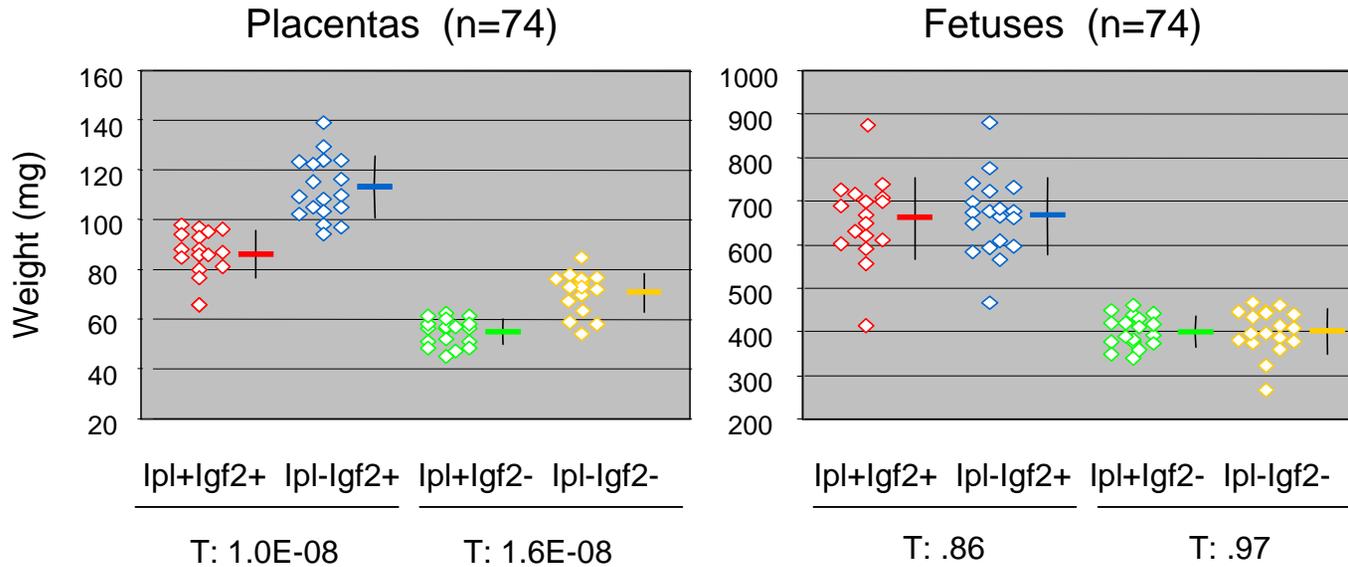


Ipl-negative

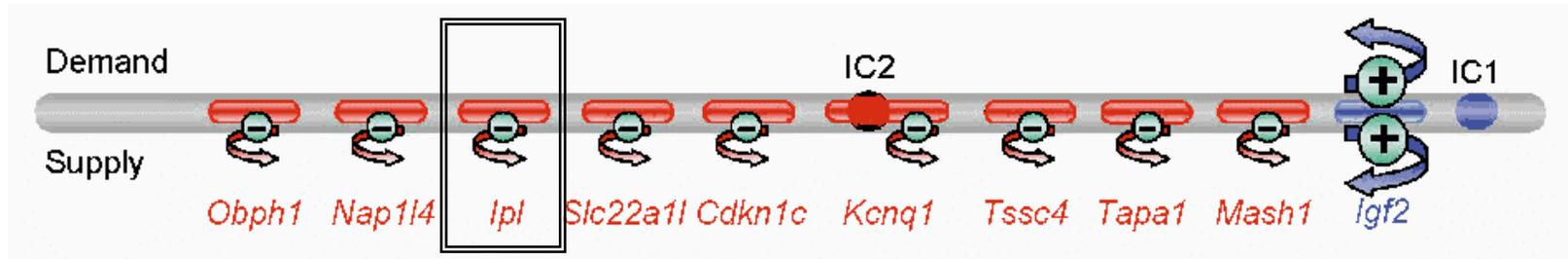
Expansion of Spongiotrophoblast in *Ipl*-null Placentas



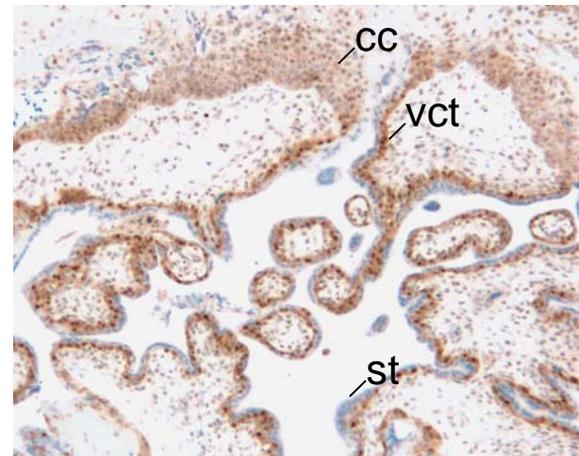
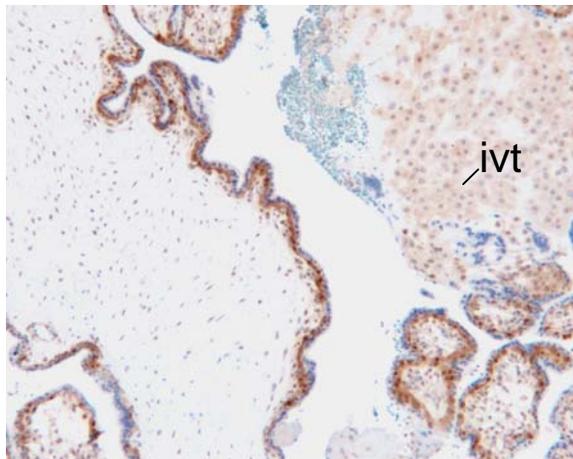
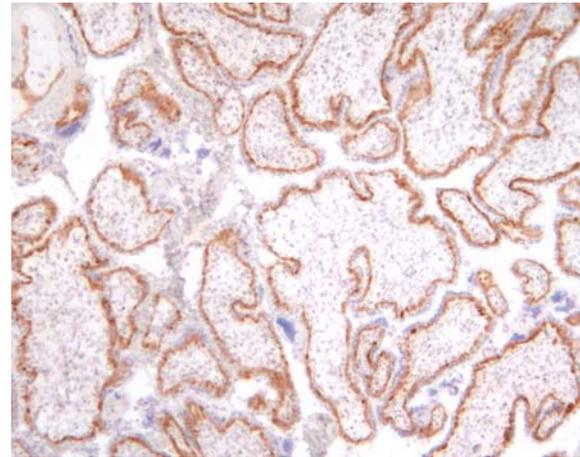
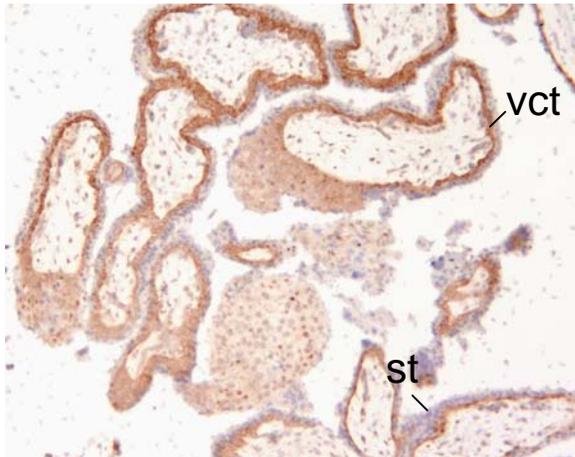
Ipl controls placental size independently of *Igf2*



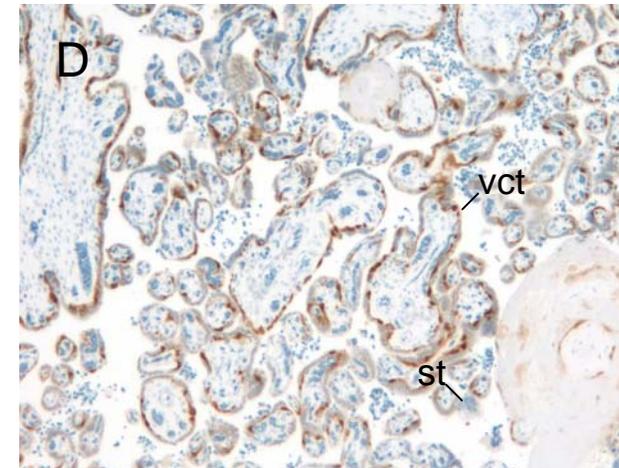
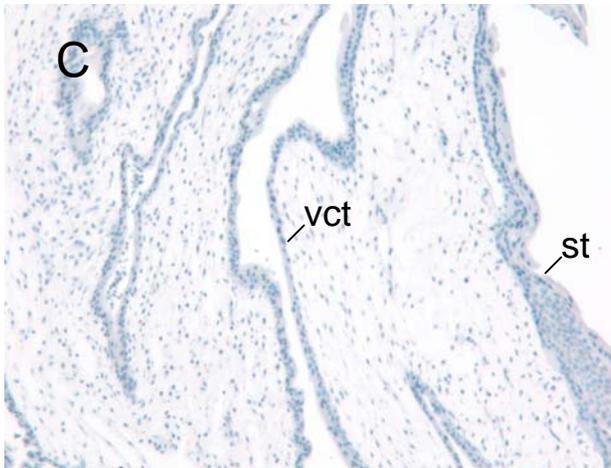
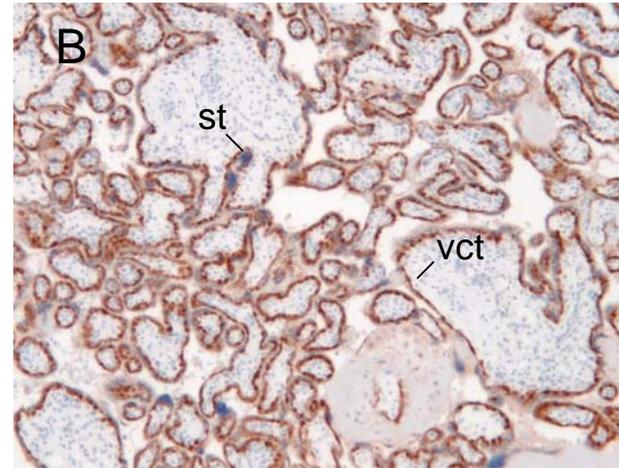
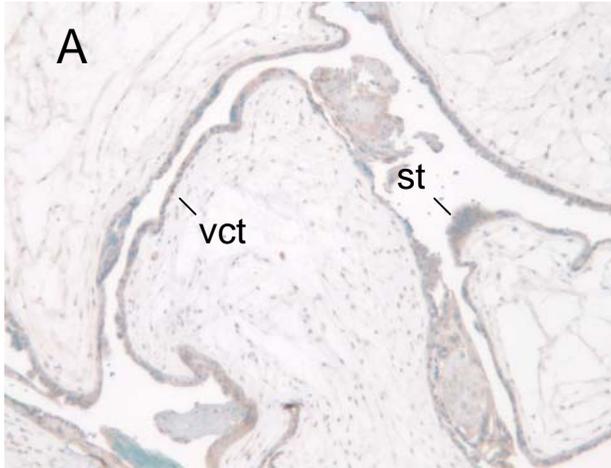
Ipl: maternal expression/paternal repression of a gene that restrains placental growth



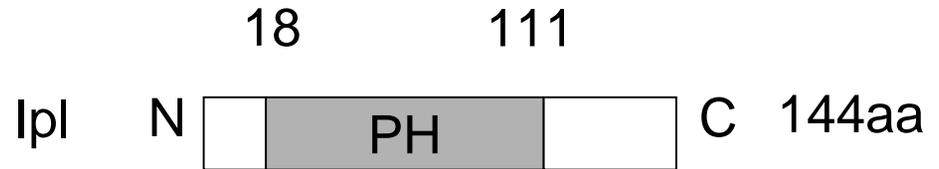
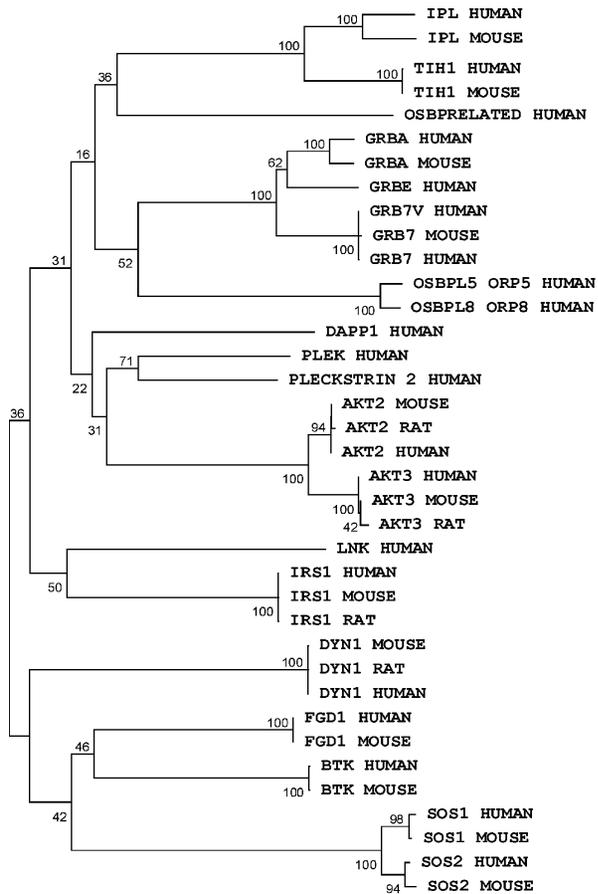
Human IPL marks villous cytotrophoblast



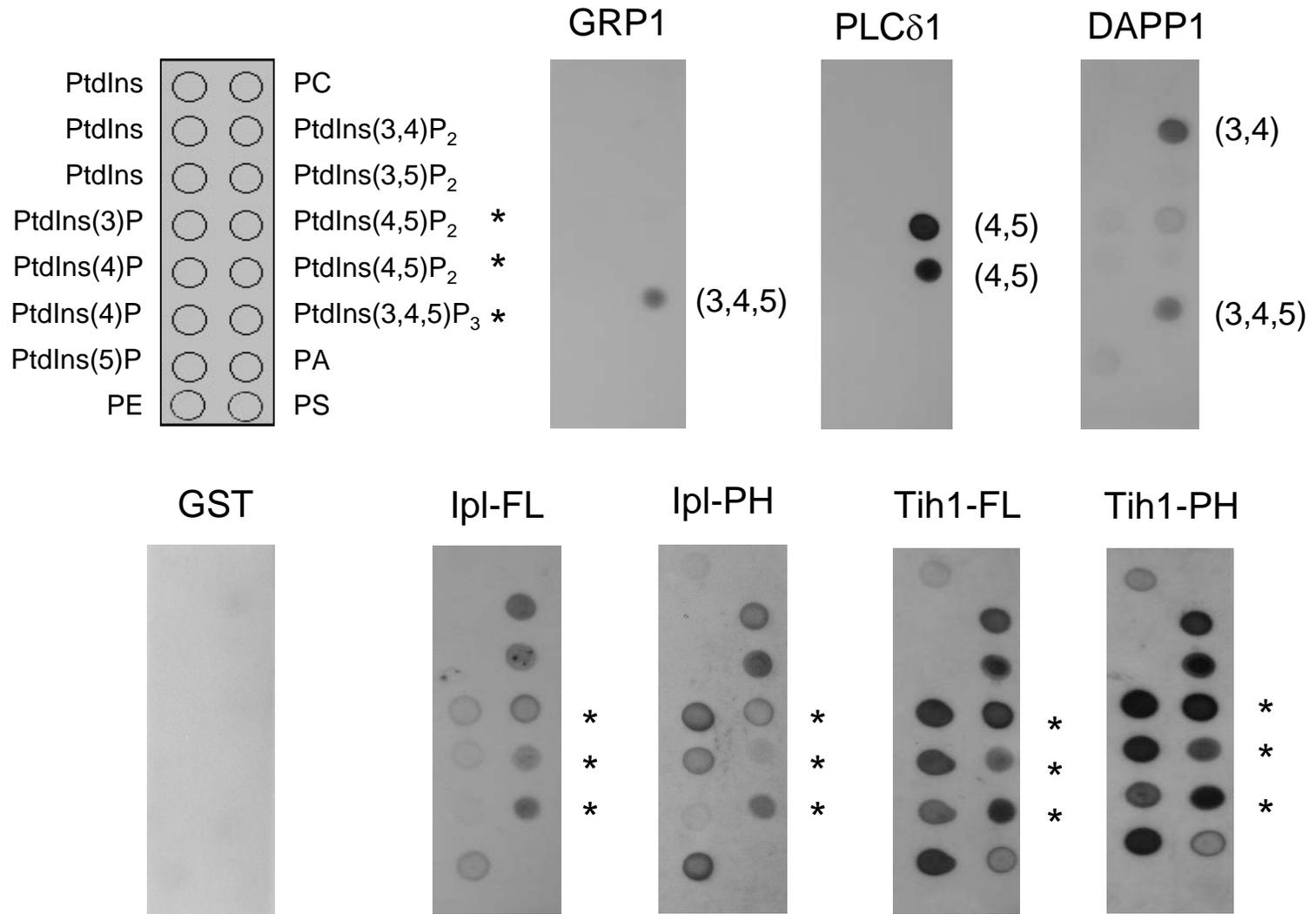
IPL is absent in hydatidiform moles



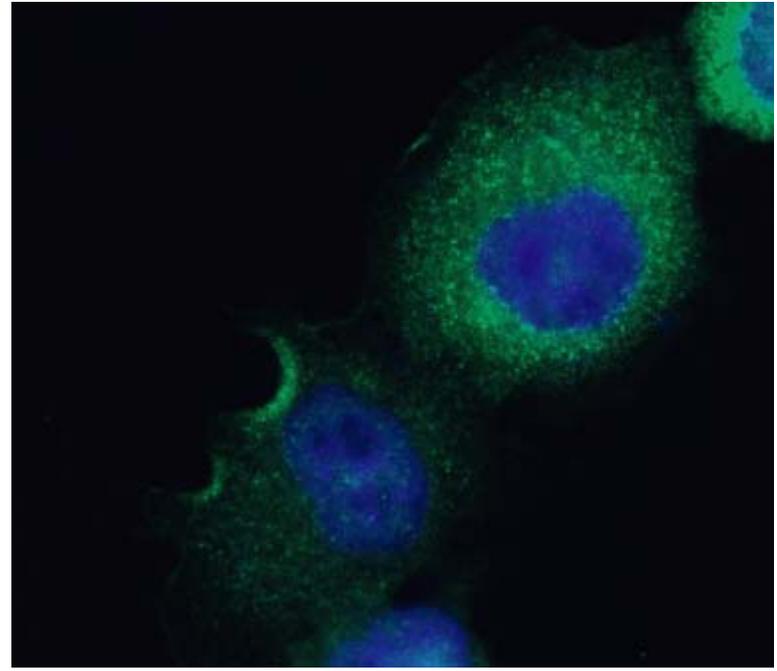
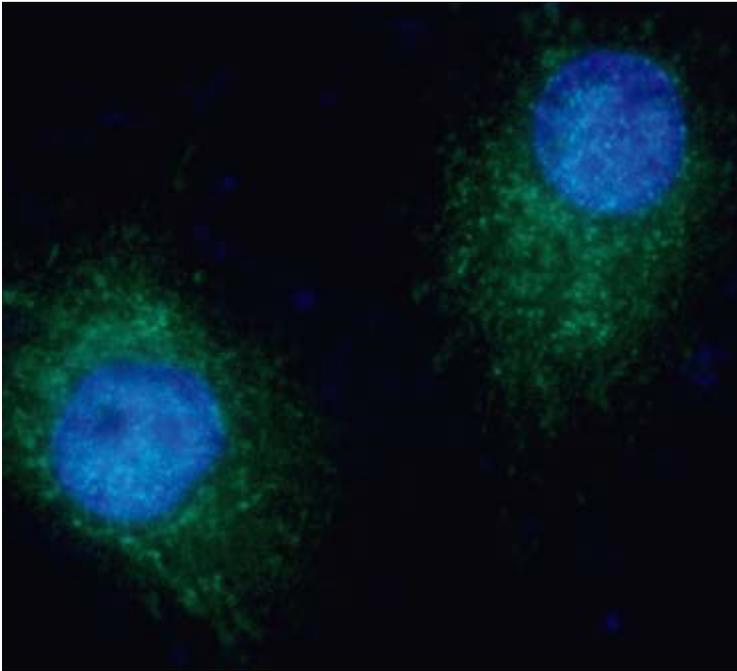
How does IPL inhibit placental growth?



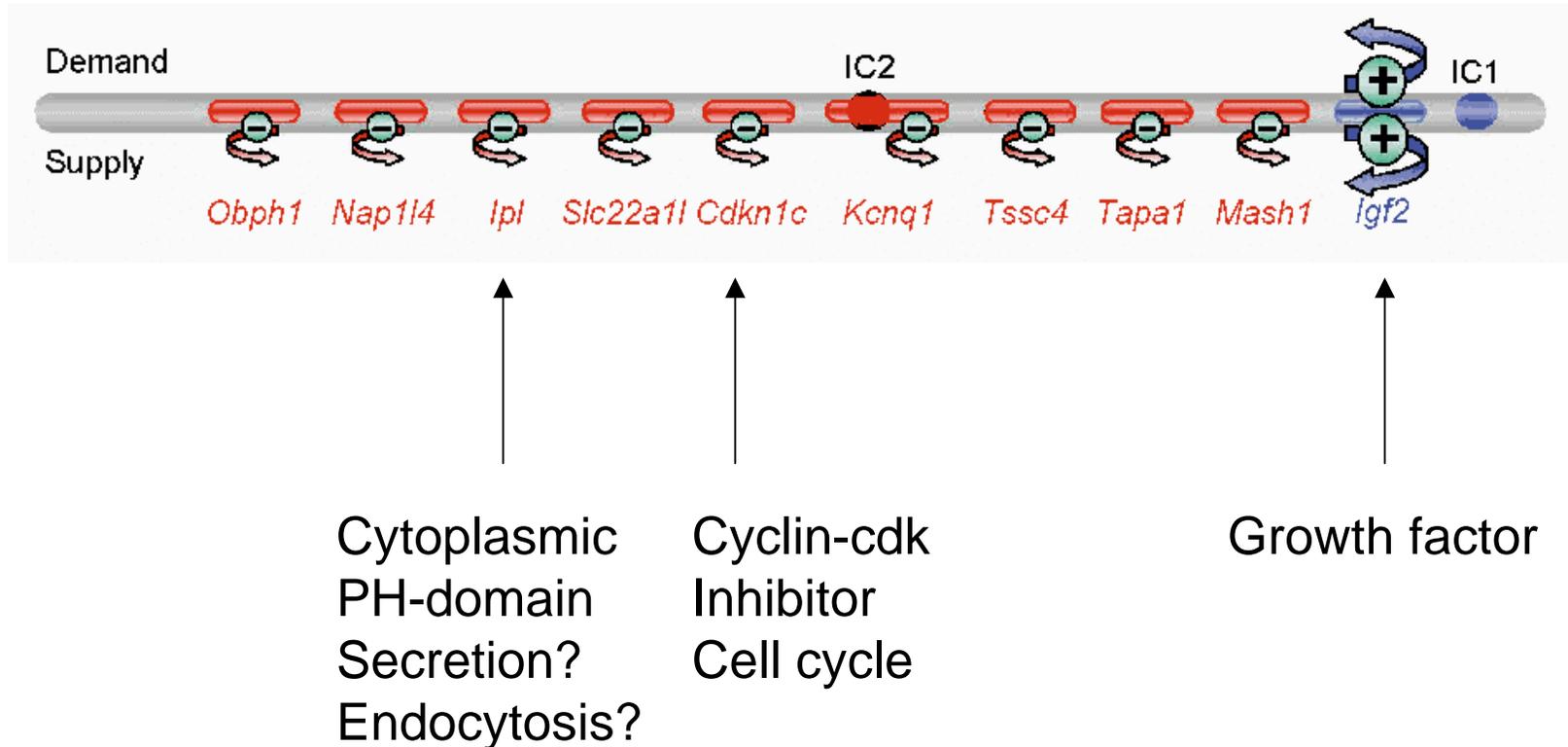
IPL is a bona fide PH-domain protein



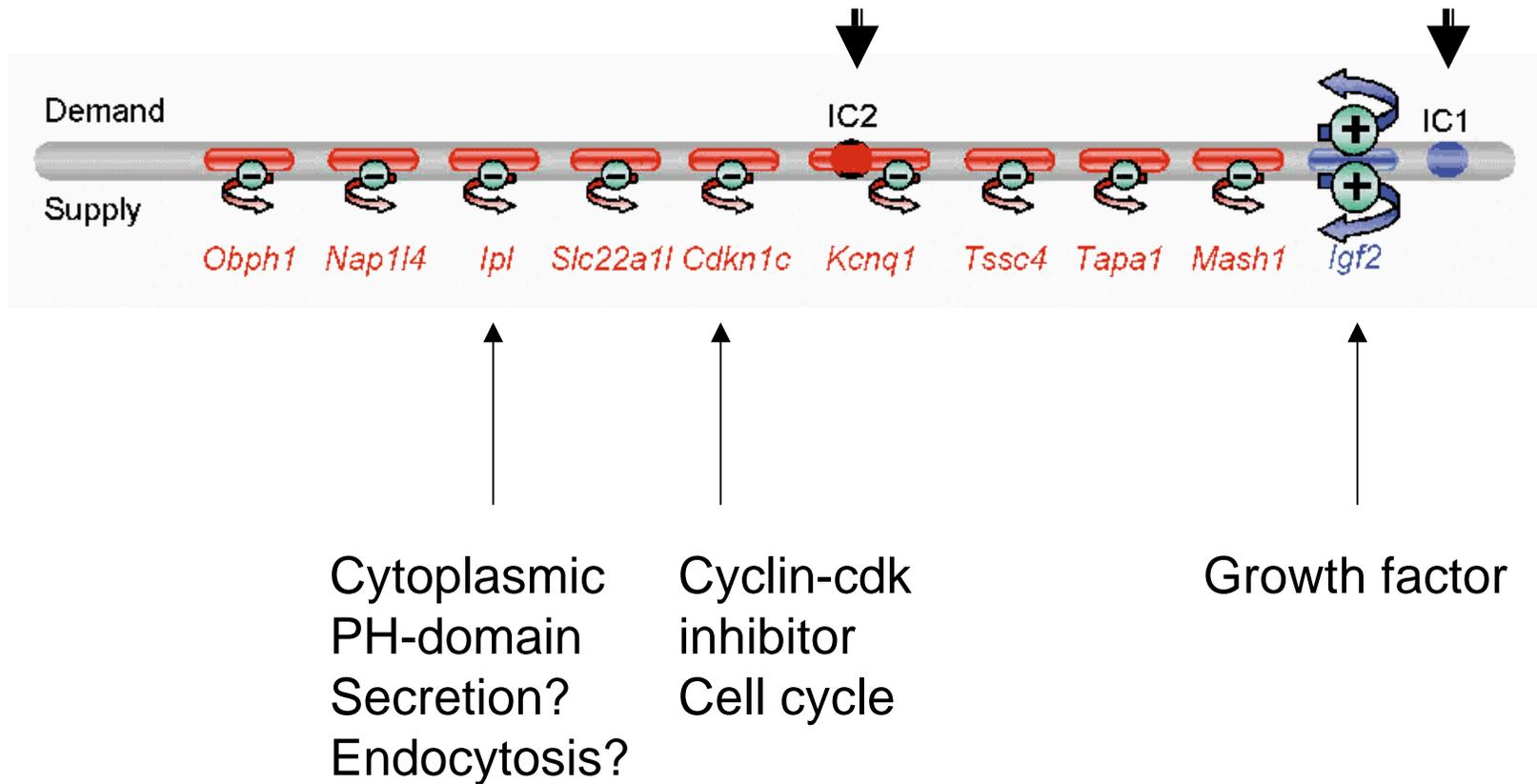
Punctate (vesicular) cytoplasmic distribution of IPL protein



Diverse biochemical pathways control supply and demand for maternal nutrients via imprinting



Q: Imprinting and IUGR?



References

Qian N, Frank D, O'Keefe D, Dao D, Zhao L, Yuan L, Wang Q, Keating M, Walsh CP, Tycko B (1997) The IPL gene on chromosome 11p15.5 is imprinted in humans and mice and is similar to TDAG51, implicated in Fas expression and apoptosis. *Hum Mol Genet* 6, 2021-2029.

Frank D, Mendelsohn CL, Ciccone E, Svensson K, Ohlsson R, Tycko B (1999) A novel pleckstrin homology-related gene family defined by *Ipl/Tssc3*, *TDAG51* and *Tih1*: Tissue-specific expression, chromosomal location and parental imprinting. *Mammalian Genome* 10, 1150-1159.

Frank D, Fortino W, Clark L, Musalo R, Wang W, Saxena A, Li C-M, Reik W, Ludwig T, Tycko B. (2002) Isolated placental overgrowth in mice lacking the imprinted gene *Ipl*. *Proc Natl Acad Sci*, 99, 7490-7495.

Saxena A, Morozov P, Frank D, Musalo R, Lemmon MA, Skolnik EY, Tycko B (2002) Phosphoinositide binding by the pleckstrin homology domains of *Ipl* and *Tih1*. *J Biol Chem* 277:49935-49944.

Saxena A, Frank D, Panichkul P, Van den Veyver I, Tycko B, Thaker H (2003) The product of the imprinted gene *IPL* marks human villous cytotrophoblast and is lost in complete hydatidiform mole. *Placenta*, in press.

Tycko B, Morison IM (2002) Physiological functions of imprinted genes. *J Cell Physiol* 192:245-258.